Regression of proximal deep venous thrombosis is associated with fibrinolytic enhancement

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Purpose: Recanalization after acute lower limb deep venous thrombosis (DVT) is well documented, but the precise mechanism and timing of these events has not been well characterized. Regression of DVT has been presumed to result from activation of the endogenous fibrinolytic system. This study was performed to compare measurements of the enzymatic components of the intrinsic fibrinolytic system (tissue plasminogen activator [tPA], plasminogen activator inhibitor [PAI-1]) with the observed morphologic changes in thrombosed venous segments using venous duplex ultrasound scanning (VDUS) at intervals after diagnosis of acute DVT.

Methods: Nineteen patients with acute DVT underwent serial VDUS to assess regression of thrombus at intervals of 1 to 2 weeks, 3 to 6 weeks, 8 to 12 weeks, and 24 to 36 weeks. The extent of thrombus in each limb was quantitated at each interval by VDUS of the residual thrombus present in each of five major axial venous segments: the common femoral, superficial femoral, profunda femoris, popliteal, and tibial veins. Thrombus scores for the group at each interval were compared with baseline scores at diagnosis to calculate the percent residual thrombus. Endogenous fibrinolytic activity was determined at the same intervals by serologic assay of the biologic activities of tPA and its inhibitor PAI-1.

Results: Thrombus regression was evident by VDUS at 1 to 2 weeks and progressed such that only 26% of residual thrombus remained at 24 to 36 weeks. Complete resolution of thrombus occurred in 10 of 18 patients (56%) who completed the 9-month study. Baseline mean tPA activity was 0.60 ± 0.07 IU/ml and increased to 1.31 ± 0.26 IU/ml at 1 to 2 weeks ($p = 0.014$). tPA activity remained significantly elevated through the 8 to 12 week interval and returned to baseline at 24 to 36 weeks. PAI-1 activity was elevated relative to an age-matched population at baseline (23.1 ± 1.8 AU/ml) but remained unchanged throughout the study period. Progression of thrombus was observed in three patients (15.8%). Patients who experienced propagation of thrombus did not have the increased tPA activity that appeared to mark activation of intrinsic fibrinolysis.

Conclusions: Regression of acute DVT begins early and continues for at least 9 months. It is accompanied by significant enhancement of the endogenous fibrinolysis, which appears to be primarily mediated by increased tPA activity. Patients who have thrombus propagation in spite of standard antithrombotic therapy may have failure of activation of endogenous fibrinolysis. (J Vasc Surg 1997;26:861-8.)

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Deep venous thrombosis (DVT) is a common ailment. Techniques for diagnosis of DVT and regimens for its therapy have been a standard part of medical care for more than a century. However, the natural history of DVT during and after medical treatment has been less well documented. Early studies suggested that recanalization of thrombosed venous segments occurred in as many as 70% of affected limbs but was a relatively late phenomenon, being seen at periods of 6 months to many years after acute DVT.[1,2] Past studies required phlebography and

were performed on small numbers of patients. Noninvasive vascular testing techniques have made serial examinations possible without risk or discomfort for the patients. Venous duplex ultrasound scanning (VDUS) allows direct imaging of major venous segments and has become the primary diagnostic technique for the initial evaluation of patients with DVT. The accuracy of VDUS for imaging proximal DVT has been essentially equal to that of contrast venography,[3] and it was logical to use this technique to evaluate the natural history of DVT. Preliminary studies of the natural history of acute DVT using VDUS have reported that lysis begins early after thrombus formation and continues through at least the first 6 months.[4-6] These studies have observed that 75% of thrombosed lower extremity venous segments will show some evidence of recanalization,[4] and as many as 50% of cases of DVT will undergo complete resolution within 6 months.[5,6] Studies using VDUS have also demonstrated that propagation of DVT, rather than clot lysis, may occur in 20% to 40% of patients despite adequate anticoagulant therapy.[6,7]

The resolution, "recanalization," or "lysis" of lower extremity DVT has been assumed to be a result of enhanced activity of the endogenous fibrinolytic system because standard antithrombotic therapy with heparin and warfarin has no proven fibrinolytic activity. However, the specific mechanism of endogenous lysis of DVT has not previously been well characterized. Endogenous fibrinolytic activity is at present best reflected by the balance between the biologic activities of tissue plasminogen activator (tPA) and its naturally occurring inhibitor, plasminogen activator inhibitor (PAI-1).[8] Enzymatic cleavage of plasminogen by tPA results in the generation of the active enzyme plasmin, which lyses fibrin clots; tPA is inactivated by formation of a complex with PAI-1. The present study was performed to characterize changes in the endogenous fibrinolytic activity in patients after acute DVT by serial measurement of the in vivo biologic activities of tPA and PAI-1. Changes in systemic endogenous fibrinolytic activity measured in patients with acute lower extremity DVT were compared with the morphologic changes (lysis or propagation) observed in the thrombosed venous segments using serial VDUS. An attempt was made to correlate the observed extent of clot lysis with the biologic activation of endogenous fibrinolytic activity and to more precisely identify the enzymatic mechanism of these changes. An attempt was also made to correlate both the biologic and morphologic findings with the clinical outcome in the study patients.

PATIENTS AND METHODS

The study group consisted of 19 men who were patients at the Baltimore Veterans Affairs Medical Center. These patients had a mean age of 52 years, and all had acute lower extremity DVT diagnosed by VDUS. All patients in this study had proximal DVT, and all DVT in the study group was unilateral. Some patients had associated calf vein thromboses (as noted below), but patients with isolated calf vein DVT were not studied. Patients with iliac or iliocaval DVT were not studied because of the relative lack of standardization of VDUS in these anatomic areas. The risk factors for DVT in the study group included malignancy (three patients), recent surgical procedure (two patients), paraplegia (two patients), prolonged immobility (three patients), history of previous DVT (four patients), nephrotic syndrome (one patient), and congestive heart failure (two patients). In two patients no obvious risk factors could be identified.

The new onset of unilateral limb edema led to initial VDUS examination in 13 of the 19 patients (68%). In two patients, unilateral leg pain suggested the diagnosis of DVT and led to VDUS diagnosis. Acute pulmonary embolism led to a secondary diagnosis of DVT in four patients (21%), and three of these patients also had lower extremity edema at the time of initial evaluation. Overall, clinically significant limb edema was present at the time of diagnosis in 16 of 19 patients (84%).

All patients in this study who had acute DVT were treated with anticoagulant therapy that consisted of continuous intravenous unfractionated heparin followed by oral sodium warfarin. Heparin treatment was begun at the time of diagnosis and was continued until warfarin therapy resulted in an international normalized ratio of 2.0 or greater (mean duration of heparin therapy, 5 days). Systemic anticoagulant therapy was continued in all patients for at least 6 months. One patient died during the study period as a result of complications of a malignancy, but there were no cases of pulmonary embolism after the initiation of anticoagulant therapy in this study group.

Extent of DVT. The initial diagnosis and classification of the extent of DVT was established in each patient using VDUS with a commercially available color-flow duplex ultrasound unit (HDI UM-9, Advanced Technology Laboratories, Bothell, Wash.). The technique of VDUS and the diagnostic criteria

Table I. Extent of initial lower extremity DVT

Involved venous segments	*No. of patients*
Common femoral, superficial femoral, and popliteal	3
Common femoral and superficial femoral	1
Common femoral	1
Superficial femoral and popliteal	4
Superificial femoral, popliteal, and tibial	1
Superifical femoral	5
Popliteal and tibial	1
Popliteal	3
Total	19

Table II. Residual thrombus and fibrinolytic activity at each time interval

Interval (wk)	*Residual thrombus (%)*	*tPA activity (IU/ml)**	*p*	*PAI-1 activity (AU/ml)**	*p*
Diagnosis	100	0.60 ± 0.07		23.1 ± 1.8	
1 to 2	95	1.31 ± 0.26	0.014	20.0 ± 2.7	0.29
3 to 6	82	1.52 ± 0.48	0.037	18.4 ± 2.5	0.21
8 to 12	60	1.29 ± 0.26	0.038	22.5 ± 1.5	0.77
24 to 36	26	0.68 ± 0.15	0.77	22.4 ± 1.9	0.86

*All values mean ± SEM.

for acute DVT have been described previously.[3] Duplex scan assessment of five specific anatomic venous segments was performed in each patient, including the common femoral vein, the superficial femoral vein, the profunda femoris vein, the popliteal vein, and the tibial veins. The quantitative extent of thrombosis in each limb studied by VDUS was calculated based on the system of Porter et al.[9] using a score assigned to each involved venous segment as follows: 0, patent; 1, subsegmental nonocclusive thrombus; 2, subsegmental occlusive thrombus; 3, occlusive thrombus throughout the entire segment. Each involved limb had a baseline quantitative "thrombosis score" based on the number of segments involved and the extent of thrombus in each segment.

Table I lists the extent of lower extremity DVT at the time of diagnosis in the study group. Thrombus was initially present in 33 of the possible 95 venous segments in these 19 limbs (35% of all segments). Thrombus was present in the common femoral vein in five patients, the superficial femoral vein in 14 patients, the popliteal vein in 12 patients, the posterior tibial veins in two patients, the peroneal veins in two patients, and the anterior tibial veins in one patient. Involvement of two or more venous segments was present in 10 patients (53%), and involvement of three or more segments was present in four patients (21%).

Regression of lower extremity DVT. Venous duplex scanning was repeated at time intervals of 1 to 2 weeks, 3 to 6 weeks, 8 to 12 weeks, and 24 to 36 weeks after the diagnosis of acute DVT. The sum of the individual scores for each limb calculated at the time of diagnosis (T_0, as described above) was considered to represent 100% for the study group. Scores were recalculated at each interval for all subjects based on the repeat VDUS, and the individual scores were then totaled at each time interval (T_N). Thrombus regression for the study group at each interval was expressed as a percent residual thrombus defined as $T_N/T_O \times 100$. The course of thrombus regression documented by VDUS at each time interval in the study is listed in Table II.

Measurement of endogenous fibrinolytic activity. Measurements of serum tPA and PAI-1 antigen (total protein) alone do not reliably predict in vivo fibrinolytic activity because these assays measure both biologically active enzyme and inactive portions bound as the tPA/PAI-1 complex. For this reason, only serum tPA and PAI-1 activity levels were analyzed in this study. Measurements of systemic tPA and PAI-1 activities were performed at the time of diagnosis of DVT in all patients. Additional assays of serum tPA and PAI-1 activities were performed at the intervals noted above at the time of repeat VDUS. Blood samples were collected in all patients using antecubital venipuncture without tourniquet-induced venous stasis, and specimens were obtained at approximately the same times of day to eliminate the known diurnal variations in tPA and PAI-1.[10] For determination of tPA activity, blood was first collected into 130 mmol/L sodium citrate anticoagulant (9:1 volume). The sample was then immediately acidified by addition of 0.5 mmol/L sodium acetate, pH 4.2 (2:1 volume), to prevent the ongoing in vitro inactivation of tPA by complex formation with PAI-1.[11] For determination of PAI-1 activity, samples were collected into modified Files solution (1 ml acid-citrate-dextrose solution, 80 μl acetylsalicylic acid solution, 10 μl prostaglandin E1) to minimize in vitro platelet activation (final dilution 1:5).[12] Samples were maintained at 4° C until centrifugation at 10,000*g* for 20 minutes, and platelet-poor plasma was stored at −80° C until assays were performed. Activity levels of tPA and PAI-1 were assayed using an amidolytic method.[13] Assays were performed in duplicate, and interassay variability was less than 5%. tPA activity was expressed in international units (IU/ml) assessed against the Second International Standard for tPA from the National Institute for

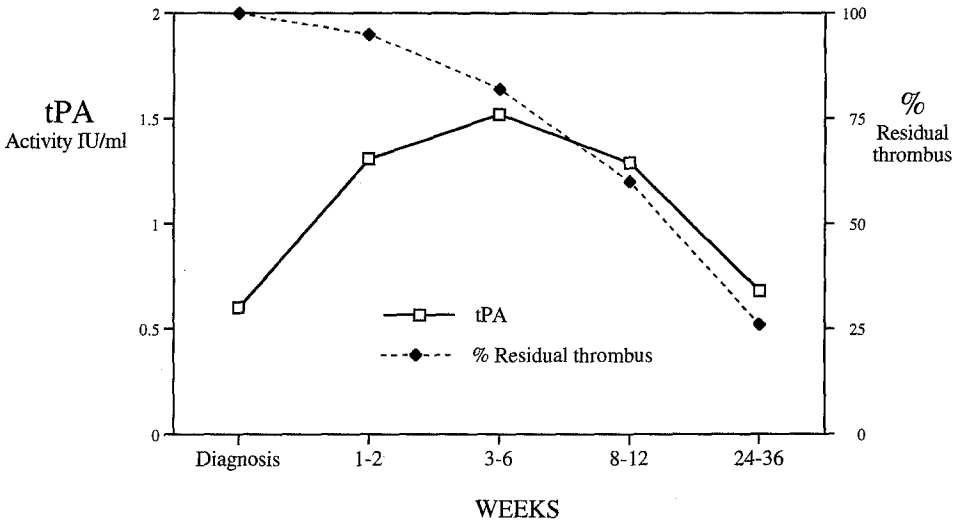

Fig. 1. Mean serum tPA activity level *(solid line)* for patients in this study at intervals after diagnosis of acute lower limb DVT. Thrombus regression observed by VDUS over the same intervals *(broken line)* is expressed as a percentage of initial thrombus burden at the time of diagnosis.

Biological Standards and Control.[14] PAI-1 activity was expressed in arbitrary units (AU/ml); one arbitrary unit of inhibitor is defined as the amount that inhibits one international unit of tPA/ml plasma.[15]

Activity levels of tPA and PAI-1 were combined for all patients at each study interval and were expressed as mean ± SEM for comparison. Changes at different time intervals were compared using Student's *t* test, and a *p* value less than 0.05 was used to determine statistical significance. This protocol was approved by the institutional review board of the University of Maryland, and informed consent was obtained from all subjects before their participation.

RESULTS

Regression of lower extremity DVT. The thrombus regression scores for the study group at each interval are listed in Table II. Lysis of lower extremity DVT began as early as 1 week after diagnosis. The thrombus regression score decreased to 95% at this first time interval and continued to decrease almost linearly throughout the study period (Fig. 1). At the 3 to 6 week interval the regression score was 82%; at 8 to 12 weeks 60% of the original thrombus load was present; and by the final 24 to 36 week period only 26% of the original thrombus burden remained.

An analysis of individual patients revealed that the thrombus scores decreased throughout the study period in 15 of the 19 limbs (78.9%). These scores increased in three patients, reflecting propagation of thrombus observed by VDUS. In two patients propagation was observed to occur in the first month after the diagnosis of DVT, and propagation was observed in one patient during the 8 to 12 week interval despite a therapeutic international normalized ratio. The scores of the patient who died remained unchanged over the short period of observation. Complete resolution of all thrombus by VDUS was noted at the end of the study period in 10 of the 18 patients who completed follow-up (55.6%).

Changes in fibrinolytic activity associated with DVT regression. Serum tPA activity levels measured during the study period are listed in Table II. The mean serum tPA activity level was 0.60 ± 0.07 IU/ml at diagnosis, which was significantly lower than tPA activity for normal age-matched volunteers in our laboratory (1.80 ± 0.23 IU/ml). Serum tPA activity increased to 1.31 ± 0.26 IU/ml 1 to 2 weeks after diagnosis ($p = 0.014$). The mean serum tPA activity levels for the study group remained significantly elevated at the 3 to 6 week interval (1.52 ± 0.48 IU/ml; $p = 0.037$) and 8 to 12 week interval (1.29 ± 0.26 IU/ml; $p = 0.038$). The activity levels of tPA returned to baseline at 24 to 36 weeks (0.68 ± 0.15 IU/ml; $p = 0.77$).

The PAI-1 activity levels for the entire study period are listed in Table II. The mean PAI-1 activity level for the study group at the time of diagnosis of lower extremity DVT was 23.0 ± 1.8 AU/ml. This

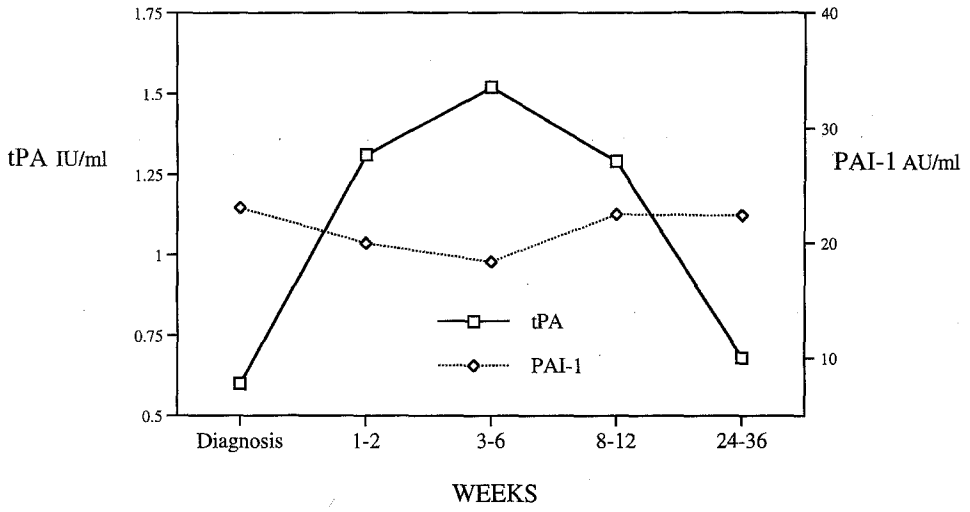

Fig. 2. Course of measured tPA activity *(solid line)* and PAI-1 activity *(broken line)* at each time interval during the study. Activation of endogenous fibrinolytic activity appeared primarily mediated by a significant increase in tPA activity during the study period.

PAI-1 activity level is significantly higher than baseline levels for age-matched normal volunteers in our laboratory (12.4 ± 1.8 AU/ml) and (with the associated lower tPA activity levels) is consistent with periods of "fibrinolytic shutdown" that have been observed in patient groups at higher risk for DVT. During the period after diagnosis of acute DVT, there were no significant changes in PAI-1 activity levels in the study group of patients at any of the follow-up intervals (Fig. 2).

Clinical presentation and outcome. No rigorous objective assessment of patients' clinical condition (e.g., limb circumference measurements) was performed as part of this analysis, and all observations were made on the basis of clinical examination at the time of diagnosis or follow-up testing. As noted above, 16 patients sought medical attention with or were noted to have significant limb edema at the time of diagnosis of acute DVT. The initial mean thrombosis score for the 16 patients with lower limb edema was 4.5 ± 0.62 and was not significantly different than the asymptomatic patients (4.0 ± 1.0). Over the study period 10 patients had resolution of limb edema, but six patients continued to have significant edema. The final mean thrombosis score for patients in whom edema resolved (0.3 ± 0.21) was significantly lower than patients who had residual edema (3.0 ± 1.0; $p = 0.05$). Baseline serum tPA activity levels were identical ($p = 0.94$) for patients who had limb edema compared with those who were asymptomatic at the time of DVT diagnosis. However, over the study period, the mean tPA levels were higher for those patients who had resolution of their edema compared with those who remained symptomatic ($p = 0.03$). No patient in this study had signs of more severe postthrombotic syndrome such as hyperpigmentation or ulceration during the period of observation.

Among the 10 patients who achieved complete clot lysis by VDUS at the end of the study period, the mean thrombosis score at the time of diagnosis (4.1 ± 0.75) was not significantly different than those patients who were observed to have residual thrombus at the completion of the study period (4.78 ± 0.79; $p = 0.70$). The mean tPA activity levels at the time of diagnosis were identical ($p = 0.85$) for those patients who had complete clot lysis compared with those who had incomplete lysis. Over the study period, tPA activity levels were not observed to be significantly higher in patients who achieved complete clot lysis compared with those who had some residual thrombus ($p = 0.68$). However, the three patients who experienced propagation of thrombus by VDUS failed to demonstrate any increase in tPA activity at the study intervals, whereas tPA activity levels were significantly elevated in the other patients.

DISCUSSION

Recanalization of occluded lower limb venous segments after acute DVT was previously considered, on the basis of studies that used repeat phlebographic

examinations performed months to years after the acute event, to be a late reaction.[1,2] VDUS has greatly expanded our ability to study the natural history of DVT because it allows virtually unlimited sequential examinations. Studies using VDUS have revealed a considerably different pattern of events in the natural history of treated DVT than had been previously suggested. Killewich et al.[6] reported evidence of lysis of thrombi and recanalization of venous segments seen by VDUS as early as the first week after diagnosis and observed that residual venous occlusion was reduced to 44% by 30 days and to 14% at 90 days. Thereafter, no significant additional lysis was observed in follow-up that continued for 9 months. Using serial VDUS to study 20 limbs with acute DVT, van Ramshorst et al.[4] calculated thrombus regression using a method similar to that in the present study. Thrombus regression was observed to occur in the first 1 to 3 weeks after acute DVT and appeared to occur at an almost exponential rate. They noted that recanalization occurred mainly in the first 6 weeks after diagnosis, but clot resolution eventually occurred in 75% of the thrombosed segments within 6 months. Caprini et al.[5] reported that complete resolution had occurred in more than 40% of thrombosed venous segments within 3 months after the diagnosis of DVT, and lysis had occurred in more than 70% of segments within 6 months of treatment. The present study would tend to confirm the observations summarized above. Some evidence of recanalization was evident by VDUS in the first weeks after acute DVT. The residual thrombosis score for the entire study group was reduced by 40% at the 8 to 12 week interval, and the residual thrombosis score rate was 26% at the 24 to 36 week interval. The rate of clot regression in our study appeared to be a more linear function over time (Fig. 1) rather than the exponential rate reported by van Ramshorst et al.[4] In addition, recanalization in our patients did not appear related to the initial burden of thrombus; the mean thrombosis scores at the time of diagnosis were not significantly different in patients who had complete clot lysis compared with those that had some residual thrombus at the end of the study period.

It has generally been presumed that recanalization after acute DVT is a result of a significant enhancement of endogenous fibrinolytic activity. However, few studies to date have reported simultaneous changes in fibrinolytic activity and the morphologic state of the thromboses. Mirshahi et al.[16] in 1988 measured serum levels of fibrin degradation products in 47 patients with acute DVT and compared these with the anatomic results of repeat phlebograms. A progressive decline in fibrin degradation products correlated well with clot resolution, presumably the result of ongoing intrinsic lysis that eventually exhausted the thrombus substrate. It is now recognized that a direct assay of tPA and PAI-1 activities are the most reliable indicators of the state of endogenous fibrinolytic activity. Northeast et al.[17] measured the activity of tPA and urokinase-type plasminogen activator (uPA) in thrombi and the adjacent vein walls in a rat model of DVT. They found significantly increased tPA and uPA activity in the thrombus and reduced tPA and uPA activity in the adjacent vein wall. Increased tPA activity was seen at 48 hours and continued to increase for at least 14 days. In the present study, significantly increased tPA activity levels were observed in the first 1 to 2 weeks after acute DVT and persisted throughout the 8 to 12 week interval. These changes were also accompanied by regression of DVT seen by direct ultrasound imaging. The tPA activity levels returned to baseline during the 24 to 36 week interval, by which time only 26% of the original quantitative thrombus burden remained. In this small group of patients, the anatomic progress of clot resolution appeared to closely parallel changes in the measured tPA activity levels.

Arcelus et al.[18] reported elevated levels of PAI-1 antigen (total protein) in patients who had incomplete resolution of acute DVT by VDUS (43% of the patients in that study). These investigators concluded that elevated PAI-1 antigen levels might be predictive of incomplete resolution of DVT. It is now known that the measurements of tPA and PAI-1 antigen alone do not reliably predict in vivo fibrinolytic activity because these assays measure both biologically active enzyme and inactive portions bound as the tPA/PAI-1 complex.[13] As noted previously, only tPA and PAI-1 activity levels were compared in the present study. Juhan-Vague et al.[19] associated recurrent DVT with a deficiency of tPA release or enhanced levels of PAI-1 as reflected in a response to venous occlusion of the arm. Stegnar et al.[20] also found that recurrent DVT occurred more frequently in patients who had elevated PAI-1 activity after venous occlusion. Elevated PAI-1 activity levels have been associated with many thrombotic complications of atherosclerosis, including myocardial infarction,[21] stroke,[22] and peripheral arterial occlusive disease.[23] No significant changes in serum PAI-1 activity levels were found in the study group at any time interval during this study. However, there was a decrease in the PAI-1 activity levels in the study group that

appeared maximum at the 3 to 6 week interval (Fig. 2), which coincided with the maximum tPA activity levels. These combined changes may have served to accelerate the process of endogenous clot lysis.

Recanalization of thrombosed venous segments does not occur universally after acute DVT. Killewich et al.[6] observed thrombus propagation by VDUS in one third of the cases despite therapeutic anticoagulant treatment, and van Ramshorst et al.[4] observed that thrombus extension occurred in one third of cases.[5] Krupski et al.[7] found that propagation occurred in 38% of patients during their initial treatment of acute lower extremity DVT, and these events could not be related to inadequate anticoagulant therapy. Propagation of thrombus was observed in three patients (15.8%) in the present study; two occurred within the first month, and one patient was observed to have clot extension 3 months after diagnosis. In all patients, propagation was observed despite apparent therapeutic anticoagulant treatment. However, in our patients the serum tPA activity levels appeared significantly lower (mean activity, 0.70 IU/ml) than other patients at the same time intervals (1.29 to 1.52 IU/ml). The small number of patients who had propagation in this study make valid statistical comparison impossible. However, the significant increase in tPA activity that was observed in other study patients appeared to be related to the temporal course of clot lysis. Because patients with clot propagation were adequately anticoagulated, it is possible that a failure of activation of the intrinsic fibrinolytic system may have contributed to the observed clot propagation.

The measured endpoints of this study did not include objectively defined clinical outcomes, but several observations are of interest. van Ramshorst et al.[4] observed that the likelihood of eventual clot lysis appeared directly related to the initial burden of thrombus. In the present study the initial burden of thrombus, as reflected by the initial thrombosis scores, did not appear to influence the likelihood of achieving either complete clot lysis or the resolution of symptomatic limb edema. The patients in this study did not have the most clinically extensive DVT that is seen, because iliofemoral thromboses were excluded. Nevertheless, they were a group comparable with other similar studies. It is evident that the patients who achieve complete clot lysis by VDUS would have lower thrombosis scores at the end of the study, but patients in this study who had resolution of edema also had significantly lower thrombosis scores suggesting the potential importance of fibrinolytic activity in the prevention of chronic venous dysfunction. Overall, patients who experienced resolution of limb edema were observed to have significantly higher tPA levels than those with persistent symptoms. However, the group of patients who achieved complete clot lysis did not have significantly higher tPA activity levels during the course of the study than those whose recanalization was incomplete. It is possible that accelerated endogenous lysis of more critical venous segments might prevent chronic dysfunction even when overall lysis is incomplete. Similarly, clot propagation in this study appeared to occur in patients who had a failure of activation of the endogenous fibrinolytic system. In the past it has been common to assume that propagation DVT or other thromboembolic complications were a result of a "failure of anticoagulation." It is possible that this instead represents a failure of the endogenous fibrinolytic system in some patients. Such a finding might support the more aggressive use of exogenous fibrinolytic therapy in some patients with acute DVT.

The patients in this study with acute lower limb DVT were observed by serial VDUS to have a progressive resolution of thrombosed venous segments that began early after diagnosis and continued over a period of 6 to 9 months. The overall 74% thrombus regression in these patients was accompanied by a significant increase in tPA activity levels, indicating activation of the endogenous fibrinolytic system. Serum PAI-1 activity levels did not change during the period of observation, which suggests that the enzymatic mechanism of clot lysis was directly related to tPA activity. In addition, the three patients in this study who had clot propagation failed to demonstrate increased tPA activity. It was also interesting to note that patients whose clinical symptoms after acute DVT resolved had significantly higher tPA activity levels. Because DVT occurs in approximately 2 million patients in the United States each year,[24] it is unlikely that a study of this size will provide definitive answers about this complex process that can be universally applied. Further study will be necessary to determine whether enhancement of naturally occurring fibrinolysis by the addition of exogenous fibrinolytic agents might be useful to prevent propagation of thrombus, as well as to increase the rate of intrinsic thrombolysis.

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